Division of Diabetes, Endocrinology and Metabolic Diseases

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Division of Diabetes, Endocrinology and Metabolic Diseases

Initiatives, Expansions or Extensions

1001 RACE/ETHNIC DISPARITIES IN THE INCIDENCE OF DIABETES COMPLICATIONS (PAS 00-028)

FY 2001 Action

This Program Announcement solicits research to investigate (1) differences among contemporary populations in the U.S., categorized by racial-ethnicity and other factors, in risk factors for complications of diabetes and in rates of these complications; and (2) the extent to which factors, including inherent metabolic and genetic variations, medical care, socioeconomic status, and behavioral factors account for these differences.

Background

Information on the incidence of diabetic complications in the U.S. is often based on community populations or large clinic populations in which the onset of diabetes occurred several decades ago. These studies generally found a striking excess of microvascular disease in minority groups, including Native Americans, African Americans and Hispanic Americans. Whether these disparities in diabetes complications continue to occur in contemporary diabetic patients is not known.

Some of the racial differences in diabetic complications may be explained by differences in availability and quality of health services. Differences in self-care practices, health care provider practices, and/or access to quality health care and prevention services may directly impinge on the frequency and magnitude of risk factors for diabetes complications and the intensity of medical care for early stages of complications to prevent progression to end-stage disease.

In addition to differences in blood glucose, lipid and blood pressure control, which may be modified by improved medical care, genetic susceptibility and other biological risk factors may contribute in unknown ways that lead to complications. This is suggested by the clustering of complications (especially nephropathy) within families and by the excess risk of retinopathy in Hispanics versus non-Hispanics that remains when the degree of hyperglycemic exposure is taken into account.

Finally, lifestyle, psychosocial factors, stress, family structure, social support, diet and culture, and socioeconomic status vary among racial and ethnic minorities and may contribute to differential risk of developing diabetes complications and progression of complications. Little is known about how these behavioral factors influence the risk of complications and the effectiveness of interventions designed to prevent or reduce diabetes complications in racial and ethnic minority groups.

Identification of these divergent etiologies and quantification of their correlation to risk have important implications for prevention and amelioration of microvascular complications. Such information might improve the effectiveness of treatment to reduce the disparities in the incidence in diabetes complications among racial and ethnic groups.

In contrast to microvascular complications, racial and ethnic minorities with diabetes often have lower rates of macrovascular disease than Caucasian population groups. The factors that account for the differing macrovascular disease rates are unknown.

Research Goals and Scope

The overall objectives are to determine (1) whether minority racial-ethnic populations continue to differ in their risk for microvascular and macrovascular complications, and, if so, (2) the reasons for these differences. It is recognized that both biologic and non-biologic factors may be operating in these populations.

Approaches may include metabolic, genetic and/or epidemiologic studies in representative populations. Advantage might be taken of extant cohort studies that may have been established for investigation of diabetes or other diseases. Alternatively, investigators may propose to start a new cohort, appropriately powered, to capture the current risks and outcomes in the era of new medications for glycemic control, blood pressure control, and lipid control.

Investigators are encouraged to incorporate appropriate surrogate markers for complications into study design to shorten the duration of studies. Such surrogate markers might include early indicators of end-stage complications (background retinopathy, albuminuria, serum creatinine, basement membrane thickening, EKG, carotid ultrasound).

Appropriate topics for investigation would include but are not limited to: (1) epidemiologic studies to determine the rates of diabetic complications in appropriate representative samples of contemporary populations; (2) studies to identify genes which might affect the development of complications in different populations; (3) state-of-the-art, hypothesis-driven metabolic studies to determine whether there are differences in metabolism, insulin sensitivity, energy expenditure, beta cell function, and body composition that might influence glycemic control and risk of complications in different populations; and (4) studies to investigate factors, such as medical care, behavior and lifestyle, and socioeconomic status, that may contribute to risk for development and progression of complications. Understanding the basis for differing susceptibilities could provide information that would lead to specific therapies likely to be useful in various subpopulations at high risk for the development of diabetes complications.

1002 RACIAL AND ETHNIC DIFFERENCES IN THE ETIOLOGY OF TYPE 2 DIABETES IN MINORITY POPULATIONS (PAS 99-166)

FY 2001 Action

This Program Announcement (PA) solicits research to expand our understanding of the underlying metabolic, genetic, epidemiologic, sociocultural, and behavioral mechanisms that contribute to the racial and ethnic differences in the etiology of type 2 diabetes mellitus in the U.S.

Background

It is well recognized that there are major differences in the prevalence of type 2 diabetes among racial-ethnic groups in the U.S. Substantial progress has been made toward identifying population-based risk factors for the development of type 2 diabetes that might lead to these racial-ethnic disparities. Such established risk factors include, for example, genetic predisposition, total and central obesity, duration of obesity, high caloric intake, and physical inactivity. Factors such as socioeconomic status, acculturation, and stress may also be important. Although these diabetes risk factors appear to operate in all racial-ethnic groups, it is not known whether specific groups are inherently different in the ways they respond to risk factors, which may lead to their differential susceptibility to diabetes. Environmental, genetic, and metabolic differences may underlie the disparity in diabetes rates, and physiological outcomes of risk factors may arise from a complex interplay of genetic and nongenetic (behavioral, lifestyle, and environmental) factors. Epidemiologic studies have documented the differing risk for diabetes among racial-ethnic groups and have established the identity of diabetes risk factors. However, with few exceptions, these studies have not been designed to examine in depth the metabolic and physiologic effects of diabetes risk factors in specific racial-ethnic populations. Consequently, there is an important need for carefully designed clinical studies to investigate these issues in representative samples of the various U.S. racial-ethnic groups.

Research Goals and Scope

The overall objective is to determine, through studies in representative U.S. populations, the reasons for disparities in the incidence of type 2 diabetes in minority racial-ethnic populations. Additionally, information that could emerge from these studies would be important for devising cost-effective approaches to phenotyping patients with type 2 diabetes and individuals at risk for this disease. The ability to characterize and identify discrete subgroups of type 2 diabetes would be essential in genetic studies of this disease. Appropriate topics for investigation might include state-of-the-art, hypothesis-driven metabolic studies in representative samples of U.S. racial-ethnic groups; the temporal relationship of changes in body weight and body composition, glucose tolerance, and insulin resistance; beta-cell function studies, such as beta-cell assessments with longitudinal follow-up, beta-cell responses to fatty acids, hyperglycemia, arginine, and insulin resistance; clinical studies of fat metabolism and insulin resistance; temporal relationships among the components of Syndrome X; and investigations of the behavioral, socioeconomic, psychosocial, cultural, family, and community factors that influence the individual's risk for developing type 2 diabetes.

1003 THE ROLE OF ENDOTHELIAL DYSFUNCTION IN DIABETIC COMPLICATIONS (PA 00-026)

FY 2001 Action

Endothelial function is known to be abnormal in diabetes and may be an early step in the development of atherosclerotic lesions. Recent work has also focused attention on the role of endothelial function in the pathogenesis of microvascular complications. This PA is intended to stimulate the application of new molecular technologies to this area. Understanding the pathogenesis of endothelial dysfunction in diabetes at the molecular and cellular level will provide new targets for pharmacologic or genetic manipulations to prevent complications of diabetes.

Background

Diabetes is the leading cause of end stage renal disease, blindness in adults, and non-traumatic lower leg amputations. In addition, individuals with diabetes have a two- to four-fold increased risk of developing, and dying from, cardiovascular disease. One in ten health care dollars in the U.S. is spent on diabetes; most of these health care costs are incurred in the treatment of macro- and microvascular complications.

Endothelial dysfunction is a key feature of diabetes and is thought to be a major cause of the associated vascular complications. Hyperglycemia itself appears to affect multiple mechanisms that increase atherosclerosis. Hyperglycemia enhances oxidation, thrombosis, inflammation, matrix production, and the formation of advanced glycation end products and other metabolites that can potentially damage the vasculature. Insulin may also play an important role in atherogenesis. Even in the absence of diabetes, patients with insulin resistance are at significantly increased risk for atherosclerosis. Insulin resistance is associated with hypertriglyceridemia and a preponderance of small, dense low-density lipoprotein (LDL). This LDL phenotype may be more susceptible to oxidative modification, a process that promotes atherosclerosis by impairing endothelial cell function, stimulating inflammation and adhesion, and promoting vascular smooth muscle cell changes. Insulin itself stimulates vascular smooth muscle cell migration, growth and matrix production, and enhances clot formation. Insulin resistance is also associated with impaired nitric oxide production.

Endothelial dysfunction may also contribute substantially to the pathogenesis of microvascular complications. Diabetic nephropathy results from changes in blood flow in small vessels with an increase in mesangial cells and excess accumulation of extracellular matrix. The earliest retinal abnormalities induced by hyperglycemia are impaired autoregulation of retinal blood flow and decreased retinal blood flow, associated with loss of endothelial-supporting pericytes from retinal capillaries. These changes are followed by endothelial cell permeability changes and retinal capillary occlusion. In diabetic peripheral sensory neuropathy, capillary closure is frequently observed in the vasa nervorum, and endoneurial blood flow and oxygen tension are reduced.

The molecular basis of endothelial cell dysfunction in diabetes is not well understood. Hyperglycemia can cause increased free radical generation and oxidative stress, which has been implicated in endothelial cell dysfunction.

Determining the effects of hyperglycemia on endothelial function, and the subsequent role of endothelial abnormalities in the development of diabetic vascular lesions, is critical to understanding the etiology and pathogenesis of the micro- and macrovascular complications of diabetes. Dissecting these pathways will provide new targets for effective therapeutic or prevention strategies.

Research Goals and Scope

Recent advances in understanding endothelial cell biology, coupled with new molecular technologies, provide powerful tools for studying endothelial function in diabetes. In addition, there is clearly a need for the development of good animal models of diabetic complications, as well as of surrogate markers for monitoring the development and progression of complications. The use of such markers would also facilitate the study of potential pharmacologic agents that could be developed, based on a better understanding of the etiology and pathogenesis of diabetic complications. Appropriate topics for investigation would include: (1) studies to determine how hyperglycemia alters endothelial and/or vascular smooth muscle cell function, including changes in gene expression; (2) studies to determine what genes modulate susceptibility of tissues to hyperglycemia-induced injury; (3) studies to understand the sequence of events in the pathogenesis of hyperglycemia-induced vascular injury; (4) studies to determine how vascular inflammation is altered in diabetes; (5) studies to determine the effects of insulin in vascular cells at the molecular and physiologic levels; (6) studies to determine how specific alterations in circulating lipids in patients with diabetes affect the development and expansion of atherosclerotic lesions; (7) studies to determine how hyperglycemia or hyperinsulinemia alter hemostasis and cellular interactions at the surface of unstable atherosclerotic plaques; and (8) studies to evaluate how antidiabetic drugs affect the vasculature and the coagulation system, and determine what impact they may have on atherosclerosis development and progression.

1004 DEVELOPMENT OF THE ENDOCRINE PANCREAS (PAS 00-015)

FY 2001 Action

This program announcement is intended to stimulate the application of advances in developmental biology, specifically in developmental genetics, embryology, and stem cell biology, to study pancreatic development. Collaborative efforts that link expertise in basic developmental biology or stem cell biology and diabetes are strongly encouraged. It is anticipated that this research will ultimately lead to a better understanding of the pathways required for the development and regeneration of the endocrine pancreas, both *in vivo* and *in vitro*. This PA, with set-asides of funds in FY 2000-2002, is intended to intensify investigator-initiated research, to attract new investigators to the field, and to encourage interdisciplinary approaches to research in this area.

Background

Type 1 and type 2 diabetes result from the anatomical and functional loss of insulin-producing beta cells of the pancreas. Replacement of these cells through regeneration or transplantation could offer lifelong treatment for diabetics. However, a major problem in implementing treatment is the lack of sufficient islet cell tissue for transplantation, and a lack of understanding of whether and how beta cells regenerate. Embryonic stem cells and other tissue-specific stem cells could potentially provide a limitless source of islet cells for transplantation therapies. Despite major advances in stem cell research and in defining specific developmental pathways in neurobiology and hematopoiesis, a fundamental understanding of the developmental pathways leading to formation of differentiated cells in the endocrine pancreas is still in its infancy.

Research Goals and Scope

Appropriate topics for investigation would include: (1) developmental genetic screens for identifying mutations in endoderm that affect pancreas development; (2) the identification of signals, signaling pathway components, and transcriptional factors that regulate endoderm specification, dorsal pancreatic bud formation, and pancreatic cell fate determination; (3) the role of cell-cell interactions, differential cell adhesion and cell motility in morphogenesis of the pancreas; (4) the role of extracellular matrix in islet cell morphogenesis; (5) molecular markers for defining all stages of pancreas development, including cell-specific markers of stem/progenitor cells of the endocrine pancreas; (6) studies examining endocrine pancreatic cell lineage, including alpha, beta, and delta cell fate determination and differentiation; (7) studies exploring the potential use of embryonic stem cells, hematopoietic, neural and other stem cells in the formation of differentiated cells of the endocrine pancreas; (8) identification of growth conditions required to generate differentiated cells of the endocrine pancreas from stem/progenitor cells; and (9) generating or using model systems for the study of regeneration of the endocrine pancreas.

1005 THE ROLE OF GROWTH FACTORS IN THE DEVELOPMENT OF DIABETES COMPLICATIONS (PAS 99-159)

FY 2001 Action
While several growth factors are already being tested in clinical trials for the treatment and/or prevention of diabetic microvascular disease, a systemic examination of the pathophysiologic role of growth factors in diabetic complications is lacking. An understanding of the tissue and cell specific expression of growth factors in affected organs, and of the molecular action of these growth factors in the pathophysiology of complications will lead to improved, more specific therapies.

Background
Diabetic complications are a major public health concern. Diabetic retinopathy is the predominant cause of blindness in adults and diabetic nephropathy is a leading cause of end-stage renal disease. Diabetes is the most common reason for non-traumatic lower extremity amputations; over 50 percent of patients with diabetes experience some degree of neuropathy. Accelerated cardiovascular disease remains the major cause of mortality in patients with diabetes.

The pathologic findings seen in diabetic complications implicate growth factors in their development. Endothelial proliferation in the eye results in abnormal neovascularization of the retina. Accumulation of mesangial matrix is the hallmark of diabetic nephropathy. Atherosclerotic lesions involve accumulation of extracellular matrix, as well as proliferation of smooth muscle cells.

Studies strongly suggest a role for vascular endothelial growth factor (VEGF) in the pathogenesis of diabetic retinopathy; however, its exact mechanism of action is not understood. Studies are needed to understand the cascade of events triggered by VEGF and how hyperglycemia leads to VEGF up-regulation.

In the kidney, transforming growth factor (TGF)-beta appears to contribute to the basement membrane thickening characteristic of diabetic nephropathy. Levels of other growth factors, including insulin-like growth factor 1 (IGF-1), fibroblast growth factor (FGF), epidermal growth factor (EGF), and platelet-derived growth factor (PDGF), are also altered; however, the role of these other growth factors in the pathogenesis of diabetic retinopathy and nephropathy is less well characterized than for VEGF and TGF-beta. Altered cytokine (e.g., tumor necrosis factor) expression may also contribute to endothelial dysfunction in diabetes.

Growth factor deficiency, rather than up-regulation, is thought to play a role in the pathogenesis of diabetic neuropathy. Levels of nerve growth factor (NGF) and IGF-1 are reduced in animals and humans with diabetic neuropathy; however, no direct connection has been made between reduced levels of neurotrophic factors and the development of diabetic neuropathy. In addition, there are multiple members of the nerve growth factor family, each of which is specifically trophic for a different neuronal population. Studies

are needed to examine not only tissue-specific but also cell-specific expression of growth factors.

Despite much suggestive evidence implicating growth factors in the development of the complications of diabetes, much remains to be determined about their role in the pathophysiology of these disorders. Little is known about how multiple growth factors might interact with each other in a specific tissue; nor is it known how growth factors interface with other abnormalities that have been implicated in the etiology of complications, including altered metabolism of polyols, accumulation of advanced glycation end products, activation of protein kinase C or increased reactive oxygen species.

Finally, the study of diabetic complications is limited by the inability to sample tissues and by the long time that it takes for complications to develop. There is clearly a need for the development of good animal models of diabetic complications, as well as of surrogate markers for monitoring the development and progression of complications. The use of such markers would also facilitate the study of potential pharmacologic agents that could be developed based on a better understanding of the etiology and pathogenesis of these complications.

Research Goals and Scope

New technologies, including the use of genetic knockouts, transgenic animals and chip array technology, provide powerful tools for studying the expression of growth factors during the development of diabetic complications, and for determining the molecular basis for their actions. Appropriate topics for investigation would include, but are not limited to: (1) studies to evaluate the tissue and/or cell specific expression of growth factors during the development of complications, including a temporal analysis; (2) studies to determine what genes are up- or down-regulated by altered growth factor expression; (3) studies to determine if growth factor signaling pathways are altered in diabetic complications; (4) studies to determine how hyperglycemia alters growth factor expression or action; (5) studies to determine how metabolic changes associated with complications interact with alterations in growth factor expression and/or action; and (6) studies to test the role of growth factors in the pathogenesis of diabetic complications using animal models (including the use of knockout or transgenic animals).

1006 INSULIN SIGNALING AND RECEPTOR CROSS TALK (PAS 99-012)

FY 2001 Action

The purpose of this initiative is to stimulate novel and innovative approaches to address the role(s) of the insulin receptor in the development, progression and treatment of diabetes and its complications.

Background

Diabetes mellitus is characterized by inappropriate regulation of serum glucose levels. Both type 1 and type 2 diabetes are characterized by insulin deficiency, with type 2 diabetes also characterized by cellular resistance to insulin action. Insulin acts through a cell surface receptor and several downstream effectors to regulate cellular growth and metabolism. Insulin target tissues also respond to hormones, growth factors, and cytokines that signal through numerous other cell surface receptors, with potential effects on insulin-dependent cellular processes. Often a cellular response represents the net response to a number of signals (cross-talk). Some of the effects of insulin receptor action can occur relatively rapidly while others may require longer-term events and include changes in gene expression. Many of the actions of insulin and its receptor, such as effects on glucose transporters, have long been under study with several ongoing efforts having produced important and major advances, but with gaps in our understanding of the underlying mechanisms of action remaining to be filled. How the integration of cell signaling in insulin-dependent tissues occurs represents an important area of investigation with implications for the pathophysiology and therapeutics of diabetes.

Research Goals and Scope

The specific objectives of this research solicitation include, but are not limited to: (1) determination of the specificity of signaling through the insulin receptor, including delineation of metabolic versus mitogenic responses; (2) elucidation of the precise mechanism of action of the insulin receptor in mediating glucose uptake in insulin-sensitive tissues; (3) signaling through growth factor, cytokine or other cell surface receptors in insulin target tissues and potential role(s) in the pathophysiology of diabetes and its complications; (4) identification of novel factors associated with cell surface receptor action in insulin target tissues which may be involved in development of diabetes, its progression; and as putative targets for therapeutic intervention; (5) structural biology of cell surface receptors involved in diabetes and its complications; (6) delineation of pathways of signaling through the insulin receptor leading to specific transcription factor(s): role(s) in the development, progression, and treatment of diabetes; (7) interactions between and among transcription factors that mediate the effects of insulin on gene expression: cross-talk with transcription factors responding to other signaling pathways; (8) signaling cross-talk between the insulin receptor and other classes of cell surface or nuclear receptors and effects on regulation of the development and/or progression of diabetes and its complications; (9) factors which regulate expression on the cell surface of functional insulin receptors, and other cell surface receptors, in diabetes and its complications; (10) identification of factors involved in cell signaling which may cause resistance to insulin action in target insulin-sensitive cells

(e.g. muscle, adipose) and novel approaches to overcoming or bypassing such resistance; and (11) the mechanism of action of nonpeptide receptor analogs and their potential efficacy as therapeutic agents.

1007 TYPE 1 DIABETES TRIALNET (TRIALNET) (RFA DK-01-003 and RFA DK-01-004)

FY 2001 Action
Two cooperative agreement RFAs will be issued--one to solicit applications from potential study sites to perform intervention studies to preserve pancreatic beta cell function and prevent type 1 diabetes, and the second to solicit applications for a coordinating center to provide clinical center coordination, analytical and statistical support for the clinical trials, as well as core support facilities. Investigators will complete the ongoing Diabetes Prevention Trial for Type 1 Diabetes (DPT-1) and participate in the design and execution of pilot and expanded studies of new agents to prevent or ameliorate type 1 diabetes, and in natural history and genetics studies in populations screened for or enrolled in these studies

Background
This initiative responds to recommendations of the Diabetes Research Working Group (DRWG) which identified additional clinical trials of immunoprevention of type 1 diabetes using antigen-specific, cytokine- or antibody-based immunotherapy as an extraordinary research opportunity. The DRWG also recommended the establishment of a national diabetes trial network of cooperative clinical research groups to create a stable, high-quality infrastructure for the conduct of effective and efficient clinical trials in diabetes.

This initiative will also allow for completion of the DPT-1, an ongoing clinical trial to determine whether use of parenteral or oral insulin in non-diabetic relatives of persons with type 1 diabetes can delay the development of diabetes. Parenteral insulin can prevent diabetes in animal models of spontaneous diabetes, can preserve beta-cell function in newly-diagnosed diabetic humans, and may delay the development of type 1 diabetes based on small pilot studies in prediabetic humans. Oral insulin can delay the onset of type 1 diabetes in the non-obese diabetic mouse. In these studies, exogenous insulin may be serving as an immune modulator or toleragen, or may be decreasing the expression of secretory granule-associated antigens from the beta cells, making them less susceptible to immune attack.

In the DPT-1, relatives of type 1 diabetic individuals are screened for islet cell antibodies of the pancreas, and if they are positive, they are staged to determine their risk for diabetes, based on further genetic, autoimmune, and metabolic factors. Individuals considered to be at high risk for diabetes are eligible for randomization to parenteral insulin (daily subcutaneous insulin and an annual insulin infusion) or to be closely monitored. Those considered to be at intermediate risk for diabetes are eligible for randomization to either oral insulin (daily capsule of human insulin crystals) or placebo.

Recruitment is approximately 96 percent complete for the parenteral insulin trial and 56 percent complete for the oral insulin trial; recruitment is expected to be completed by the end of 2002. Participants are to be followed for at least two years. DPT-1 is presently funded through August 2001. Nine clinical centers and associated networks of

recruitment/retention sites are participating in the DPT-1. Core support facilities include the operations coordinating center, data monitoring unit, laboratories, compounding and distribution pharmacies, and clinical cost reimbursement system.

To plan for future TrialNet studies in the prevention of type 1 diabetes, the NIDDK and DPT-1 investigators have convened meetings to discuss potential cohorts and agents, eligibility criteria, and outcome measures. Examples of potential cohorts include new onset type 1 diabetic subjects identified through the DPT-1 and individuals who have other markers of diabetes but who are ineligible for DPT-1. Examples of potential agents include antigen-based therapies such as recombinant human GAD65 and the heat shock protein hsp60 p277 peptide, monoclonal antibodies such as anti-CD3 and anti-CD25, and certain cytokine-based therapies. Multiple pilot studies could simultaneously test promising agents, and on the basis of these, expanded intervention studies might be launched.

The established DPT-1 network is an excellent platform on which to build an enhanced network that would comprise the TrialNet. Expansion of the number of recruitment sites would enhance recruitment of subjects for the DPT-1 and for future TrialNet studies. The DPT-1 population and populations identified by the TrialNet may be fruitful groups to study predisposing genes to type 1 diabetes and diabetic complications. Samples and associated data from participants of TrialNet may be entered into genetic repositories for use by investigators inside or outside the TrialNet.

Research Goals and Scope

The current number of clinical centers and associated networks of recruitment/retention sites of DPT-1 will be expanded up to approximately 20 in order to complete the DPT-1 and begin simultaneous pilot, feasibility, and efficacy studies of new agents to preserve pancreatic beta cell function. Core facilities will support the completion of the DPT-1 and new studies within TrialNet. The newly constituted Steering Committee will select pilot and expanded intervention studies, as well as natural history and genetics studies, and will develop a mechanism to evaluate new proposals submitted to the TrialNet once initial awards have been made.

1008 PREVENTION AND TREATMENT OF TYPE 2 DIABETES IN CHILDREN AND ADOLESCENTS--CLINICAL CENTERS AND COORDINATING CENTER (RFA DK-01-010 and RFA DK-01-011)

FY 2001 Action
Two cooperative agreement RFAs will be issued--one to solicit applications from potential study sites to perform clinical trials for the prevention and treatment of type 2 diabetes in children, and the second to solicit applications for a coordinating center to provide clinical center coordination, and analytical and statistical support for the clinical trials.

Background
Type 2 diabetes is characterized by insulin resistance and impaired insulin secretion, although its precise etiology and pathogenesis are only incompletely understood. The public health impact of type 2 diabetes is enormous.

Clearly associated with aging and obesity, type 2 diabetes has traditionally been considered a disease of adults. Children are assumed to have type 1 diabetes, an autoimmune disease. However, recent epidemiologic data reveal an increasing number of cases of type 2 diabetes in the pediatric population, especially among adolescents and in certain minority populations. In general, population-based screening data are not available. Data culled from diabetes clinics in several locations suggest that the percentage of children diagnosed with diabetes who are classified as having type 2 diabetes has risen from less than 5 percent (prior to 1994) to 20 to 30 percent (after 1994). The increase in type 2 diabetes in children is presumed to be a consequence of widespread obesity and decreased physical activity.

Data from NHANES III suggest that up to one-third of adults who have type 2 diabetes may go undiagnosed. A similar situation may exist with children. In fact, the diagnosis of type 2 diabetes in children is often made because of routine laboratory screening being conducted as part of a school physical and not because the child presents to a health care provider with specific complaints. Thus, many children who do not receive such screening may go undiagnosed until they become symptomatic, at which time they may have been hyperglycemic for many years and are at high risk of developing diabetic micro- and macrovascular complications. In addition, significant numbers of children may not have frank diabetes, but may be at high risk of developing diabetes based on the presence of insulin resistance, impaired fasting glucose or impaired glucose tolerance. It is, therefore, imperative to establish appropriate screening criteria and effective primary prevention programs to avoid a potential major public health burden.

The majority of children with type 2 diabetes are in the pre-adolescent or adolescent age range. The adolescent period presents special challenges to health care providers and families when attempting to promote behavior and life style changes. Prevention and treatment programs must also consider cultural differences among racial and ethnic groups that may influence acceptance of medical regimens. This is especially important for type 2 diabetes in children, which disproportionately affects minority groups.

When children do develop diabetes, efficacious therapy is needed to maintain euglycemia in order to prevent the development of complications. Diabetes is currently estimated to cost the U.S. health care system approximately $98 billion annually. Much of the cost is related to the micro- and macrovascular complications of diabetes. Since the development of complications is related, in part, to the duration of diabetes, children represent a population at high risk. Unfortunately, the drugs currently approved for use in adults with type 2 diabetes have not been systematically studied in children. Thus, treatment options for those children diagnosed with type 2 diabetes are restricted by the lack of data on the use of such pharmacological agents. Optimal treatment of type 2 diabetes in children, as well as in adults, should go beyond merely achieving euglycemia. Preserving beta cell function in children with impaired glucose tolerance or type 2 diabetes is of critical importance. Thus, clinical trials are needed to establish appropriate and effective treatment regimens for children with type 2 diabetes.

Research Goals and Scope

This RFA solicits investigator-initiated clinical trial proposals for the primary prevention and treatment of children (6 to 18 years of age) with type 2 diabetes. The trial proposed should involve either primary prevention or treatment, and the application must contain a rationale for the intervention chosen.

Primary prevention trials should focus on cost-effective, school or community based interventions with the potential for broad, population-wide application. Treatment trials may include lifestyle changes and/or pharmacologic therapy. A desirable goal of a treatment trial should be the assessment of beta cell function (i.e., insulin secretion), as well as glucose control.

Based on peer review, awards will be made to those centers whose proposals are judged to be of high scientific merit. A Steering Committee will then be created, comprised of the Principal Investigator of each study site, the head of the Coordinating Center, as well as an NIDDK representative. The Steering Committee will meet during the planning phase of the cooperative agreement to design the actual study protocols. It is anticipated that the Steering Committee will develop one, multi-arm trial for the treatment of type 2 diabetes in children to be carried out at multiple sites, to insure an adequate sample size, as well as geographic and racial/ethnic diversity. At least one, but possibly more, primary prevention protocols will be developed. The prevention trial ultimately designed by the Steering Committee may involve a standard protocol with variations based on the need for cultural sensitivity at different sites, or the Steering Committee may opt for several distinct prevention trials. If multiple prevention trials at different sites are carried out, the Steering Committee will establish standardized entry criteria, clinical assessments and outcome measures so that all the trials can be compared.

1010 BETA CELL BIOLOGY CONSORTIUM

FY 2001 Action

The NIDDK proposes to establish a Beta Cell Biology Consortium for the purpose of intensifying investigator-initiated research, attracting new investigators into the field, encouraging interdisciplinary approaches to research in this area, fostering the application of basic research to generate new research tools and approaches for the diagnosis, treatment, and cure of diabetes, and establishing a comprehensive database for the beta cell. Through the Consortium, individual Beta Cell Biology Programs will have access to information, resources, technologies, expertise, and reagents that are beyond the scope of any single research effort.

Background

The beta cell of the endocrine pancreas plays a critical role in the pathogenesis of both type 1 and type 2 diabetes. Thus, having a comprehensive understanding of the molecular basis of beta cell development and function should generate new research tools and provide critical insights into the prevention and treatment of diabetes.

In FY 1999 the NIH initiated a project entitled, "Functional Genomics of the Developing Pancreas" which will identify novel genes controlling the differentiation of beta cells and provide information useful in developing strategies in beta cell replacement and modulation of autoimmune beta cell destruction. The ongoing program will develop comprehensive microarrays of genes expressed in the beta cell allowing investigations of global gene expression in islets from mouse models of diabetes and in islets from humans. An expression profiling database is under development that will allow all investigators access to these data, and will promote progress in the differentiation and regeneration of beta cells.

One of the goals of the current RFA is to build upon the foundation of the ongoing Functional Genomics of the Developing Pancreas Consortium through the initiation of a series of complementary projects to further understand the function of the beta cell, and to generate reagents and assays needed for the development of novel cellular therapies for diabetes. In addition to the Functional Genomics of the Developing Pancreas Consortium, major scientific advances and technological breakthroughs in basic disciplines such as developmental biology, stem cell biology, mouse genetics, imaging, bioengineering, and bioinformatics demand that a multifaceted, interdisciplinary, and coordinated, collaborative approach on several fronts be utilized to generate key reagents, assays and new strategies for the diagnosis, treatment and prevention of type 1 and type 2 diabetes.

Research Goals and Scope

The NIDDK will select as components of the Beta Cell Biology Consortium approximately five Beta Cell Biology Program applications, each supporting a multidisciplinary team. A Beta Cell Biology Program could consist of several collaborating investigators representing one or more institutions. Programs must address at least one of six targeted scientific areas described below, however, applications

addressing more than one targeted area are highly encouraged. Each program must include a plan that addresses the need for both a bioinformatics component, and data sharing, within the broader consortium of U01s.

A. Beta Cell Development: Research leading to an understanding of the developmental pathways is required to produce a fully functioning pancreatic islet and insight into the mechanisms underlying regeneration of beta cells in the pancreas.

B. Prospective Identification and Purification of Pancreatic Stem/Progenitor Cells: Tissue specific stem cells potentially could provide a limitless source of islet cells for transplantation therapies. Generating reagents such as antibodies to stem cell surface markers, and the use of these antibodies to isolate and purify these cells using flow cytometry, would facilitate development of a cellular therapy for diabetes involving stem cells.

C. Development of Clonogenic Assays for Evaluating Potential Stem Cells: To characterize stem/multipotential progenitor cells, it is necessary to have quantitative assays (both *in vitro* and *in vivo*) in which to assess the ability of these cells to: (1) give rise to multiple lineages; (2) self-renew; and (3) reconstitute a cellular compartment.

D. Evaluation of Pancreatic Islets for Transplantation: Use of DNA array technology, for assessing the quality, purity and viability of pancreatic islets isolated for transplantation as therapy for type 1 diabetes, may provide a method to predict which islet preparations will survive upon transplantation. Such assays would be useful for comparison of methods of islet isolation and for development of improved approaches to islet isolation.

E. Functional Imaging of the Beta Cell: Studies to validate new therapeutic approaches to prevent or delay immune destruction of beta cells would be greatly facilitated by the ability to image the pancreatic beta cell in patients, and detect changes in cell number, cell mass, function and metabolism. Identification of cell surface markers differentially expressed in the beta cell and development of tagged antibodies to these cell surface markers would be useful in development of modern molecular and functional imaging techniques to allow beta cells to be visualized *in vivo.*

F. Cell Culture Model of the Human Pancreatic Beta Cell: This supports research to develop a beta cell model with the following salient features: (1) stably maintain its physiologic responsiveness to glucose and other secretagogues; (2) accurately reflect *in vivo* signaling through cell surface and nuclear receptors relevant to the regulation of insulin production and secretion; (3) maintain responsiveness to growth factors and cytokines normally active in the development and maintenance of the pancreatic beta cell; and (4) retain contact growth inhibition as in the *in vivo* situation.

1012 BETA STEM CELL SURFACE MARKERS

FY 2001 Action

Development of antibodies directed at beta stem cell surface markers would have important commercial applications. Antibodies against beta stem cell markers would be useful in isolating stem cells for potential use in islet replacement therapy. This solicitation will request Small Business Innovation Research proposals to develop reagents needed for these applications.

Background

Type 1 and type 2 diabetes result from the anatomical or functional loss of insulin-producing beta cells of the pancreas. Replacement of these cells through transplantation could offer lifelong treatment for diabetes. A major obstacle in implementing treatment is the lack of sufficient islet cell tissue for transplantation. Tissue specific stem cells potentially could provide a limitless source of islet cells for transplantation therapies.

Generating reagents such as antibodies to stem cell surface markers would facilitate development of a cellular therapy for diabetes involving stem cells. In general, stem cell populations are rare, and represent only a small fraction of the total number of cells in a developing or regenerating tissue, and thus need to be greatly enriched. Methodologies using monoclonal antibodies to cell surface markers have been used to enrich and purify hematopoietic and neural stem cells. For example, common myeloid, as well as common lymphoid progenitors from mouse or human have been isolated prospectively, and then purified and characterized using antibodies to cell-surface markers and flow cytometry.

Despite recent advances in understanding some of the transcriptional regulators important in pancreatic development, major obstacles for isolating a stem/progenitor cell population from the pancreas exist, including the lack of appropriate cell surface markers and only a cursory understanding of the lineage of beta cells during regeneration and development. Overcoming these obstacles would greatly facilitate efforts to isolate, purify, and characterize stem/progenitor cells of the endocrine pancreas.

Research Goals and Scope

To facilitate the prospective identification and purification of mammalian stem/ progenitor cells from the pancreas, proposals are sought for the development of antibodies to cell surface markers on these specific cell populations. Applicants should delineate the source of cells for antibody development, and the method of characterization of antibodies. Proposals should include the development of a quantitative, clonogenic assay, *in vivo*, similar to what exists for studying hematopoietic and neural stem cells that will allow the characterization of potential stem/progenitor cells after their isolation.

This solicitation encourages the development of antibodies to cell surface markers specific for stem/progenitor cells of the pancreas, and the use of these antibodies to isolate and purify these cells using flow cytometry. Sources for isolation of appropriate mouse or human tissue for generating cell surface antibodies may include: dissected

mouse or human fetal tissue, such as developing foregut or pancreatic buds; purified endodermal precursors derived from adult or fetal liver, gut, lung, or other endodermal-derived tissue; stem/progenitor cells isolated from the regenerating pancreas; isolated pancreatic precursor cells from genetically defined mouse models, such as enrichment of cells from transgenic lines in which green fluorescent protein (GFP) is driven by a pancreas-specific, developmentally regulated promoter). In addition, this solicitation will encourage utilization of the database developed by the Functional Genomics of the Developing Pancreas Consortium to identify potential cell surface markers specific to stem/progenitors of the developing pancreas from which antibodies could be generated.

1014 DIABETES GENOME ANATOMY PROGRAM

FY 2001 Action

The proposed FY 2001 initiative would expand the Diabetes Genome Anatomy Program (DGAP) to include all of the major organ systems affected by diabetes and its complications. The development of array libraries and bioinformatics tools applied to normal and pathological conditions of the endocrine, renal, cardiovascular, genitourinary, musculoskeletal, and peripheral nervous systems should contribute to our understanding of human physiology and spur development of diagnostic tools and therapeutic approaches aimed at reducing the burden of diabetes and its complications.

Background

Major progress has been made in understanding basic insulin signaling pathways, glucose metabolism, and interactions between multiple tissues in the maintenance of glucose homeostasis and in the development of diabetes and its complications. Nevertheless, current approaches to this problem are inadequate to address the growing health burden of diabetes in a reasonable timeframe. Over the past decade the rapid progress of the Human Genome Project and extraordinary technology developments have led to an explosive growth in our knowledge of genetics and genetic basis of disease. Adequate resources are now available to apply a more systematic and coordinated approach to the complex problem of pathogenesis of diabetes and to develop more effective therapies for this disease. The NIDDK has initiated a functional genomics program, DGAP, which has initially focused on the endocrine pancreas and has as a major goal development of tools that are targeted to restoration of pancreatic beta cell function. This program involves a consortium of investigators at Washington University, the University of Pennsylvania, and Harvard University with expertise in pancreatic development, functional genomics, and bioinformatics. This program will catalog all genes expressed in the developing mouse pancreas and make clones available through the IMAGE consortium. The Center for Bioinformatics at University of Pennsylvania has developed a website which contains a database of pancreatic genes as well as tools to aid researchers in expression profiling, gene discovery, and promoter analysis. Microarrays developed by this consortium should prove valuable for studies of islet cell development, bioengineering of beta cells, and stem cell biology.

Research Goals and Scope

The major goal of DGAP should be the creation of a complete data set of the genes and gene products involved in insulin secretion, insulin action, insulin resistance, and the predisposition to diabetes. The project should allow for an understanding of how these molecules work, and what leads to their alterations in expression sequence and/or function in the diabetic state. This knowledge is necessary for the successful quest to prevent diabetes and development of more effective and specific modes of therapy.

Specific Aims:

A. Creation of a catalog of all of the genes expressed in various tissues which play a role in diabetes or related disorders, including insulin action or resistance, classical insulin-responsive tissues, islet cells and other potentially insulin-responsive tissues.

B. Selection of appropriate human and rodent material for creation of DNA, RNA, and protein repositories large enough to perform the appropriate genetic and protein analysis. These samples should come from individuals or animal models in which there is excellent metabolic phenotyping to allow a full analysis of intermediate phenotypes of diabetes and its associated disorders. This should include people with developed diabetes, as well as those with insulin resistance of other causes and defined pre-diabetic states. It should also include as wide a range of tissues as feasible including those involved in diabetic complications.

C. Development of a systematic, coordinated effort to use all modern technologies--including SNPs, direct sequencing and gene expression arrays--to scan these samples to identify potential changes in the genes involved in diabetes, including determination of the range of sequence and expression variation in these genes, or the proteins they encode, which might affect the risk of diabetes or one of its component parts such as insulin signaling. In addition, potential diabetes-related genes should be identified by studies of subtraction libraries and other measure of quantitative gene expression pattern in different tissues from normal, pre-diabetic, and diabetic individuals.

D. Using the above information, develop a high-throughput technology, such as a "diabetes DNA chip," that could be applied to determining the risk of diabetes and related disorders in large population studies or used in basic cell biology studies.

E. Support parallel proteomics and structural biology efforts, as well as pilot and feasibility studies, for application of new technologies to the study of the genetics of diabetes and the role of hormonal signaling defects in this disease, especially those which take advantage of the new genetic information.

1015 GENE THERAPY FOR TYPE 1 DIABETES AND ITS COMPLICATIONS (RFA DK-01-006)

FY 2001 Action

The NIDDK, the National Institute of Allergy and Infectious Diseases (NIAID), and the National Heart, Lung, and Blood Institute (NHLBI) are soliciting applications to develop gene therapy approaches for the treatment of diabetes and/or its complications. Gene therapy is a promising technology to introduce exogenous genes into somatic cells that will alter the cell's properties. On November 8 and 9, 1999, the NIDDK, NIAID and NHLBI along with other NIH institutes sponsored a meeting, entitled, "Gene Therapy Approaches for Diabetes and Its Complications," to discuss possible approaches for using gene therapy to treat either diabetes or its complications. One of the recommendations from the meeting was to support additional studies to develop novel approaches using gene therapy for the treatment of diabetes and its complications.

Background

Over the last ten years, gene therapy techniques have been developed for introducing genes into somatic cells that alter the properties of these cells. Recently, several successful reports suggest that gene therapy may be an appropriate treatment for certain conditions. There are many approaches to interfering with the development of type 1 diabetes and to treating the complications resulting from both type 1 and type 2 diabetes that would appear to be amenable to gene therapy technology. The purpose of this RFA is to encourage development of gene therapy approaches for type 1 diabetes and its complications, and to test these in appropriate animal models or small pilot studies.

Type 1 diabetes results from the immune destruction of the beta cells in the pancreas. Therefore, methods that interfere with the development of autoimmunity or the immunodestructive process would prevent the development of type 1 diabetes. There seems to be sufficient understanding of type 1 diabetes immune-mediated beta cell killing to devise gene therapy approaches that interrupt the inflammatory process. It may also be possible to interfere directly with the apoptotic pathways within the beta cell that result in its death. This use of gene therapy will not correct a defective genetic makeup but rather will interrupt the progression of disease pathogenesis.

Ongoing research at the preclinical level suggests that islets expressing certain ligands or immune suppressive cytokines have an improved survival. This is a novel and hitherto uncharted area of research that deserves further exploration. Recently, a novel approach of generating beta cells *in vivo* has been tested in an animal model. The introduction of the transcription factor, PDX1, into hepatocytes resulted in the transdifferentiation of hepatocytes to beta cells (Nature Medicine 6:568-572, 2000). The exploration of this and other transdifferentiation strategies may also yield novel ways to treat type 1 diabetes.

Long-term complications of diabetes include nephropathy, retinopathy, neuropathy, accelerated cardiovascular disease, impaired wound healing, altered gastrointestinal and bladder function, and periodontal disease. Since glucose management remains a difficult

problem, complications from diabetes continue to be a high priority area for development of novel treatments. Gene therapy approaches seem promising in the selected areas of micro and macro vascular disease; neuropathy and wound healing and other approaches need to be explored.

Research Goals and Scope

Applications should focus on the development of gene therapy approaches for the treatment of type 1 diabetes and its complications. Although delivery of insulin by gene therapy is one possible method to treat diabetes, this approach is complicated by the requirement for rapid and tight regulation of insulin secretion to glucose levels. Such studies may be premature with our current technology. The following relevant topics are examples and should not be construed as required or limiting: (1) To investigate gene therapy strategies to induce tolerance to beta-cell antigens; (2) to investigate novel strategies such as T-cell homing to deliver immunosuppressive genes; (3) to investigate altering cytokine gene expression in order to suppress the inflammatory process; (4) to develop vectors that are targeted to the pancreatic beta-cell to deliver genes that interfere with its immunodestruction; (5) to investigate the expression of protective genes in beta cells to prevent immunodestruction; (6) to explore the use of altered expression of other genes in the glucose metabolic pathway for their therapeutic potential to complement the effects of insulin; (7) to investigate expressing genes involved in mouse and human beta-cell differentiation to determine their role in transdifferentiation of cell types such as hepatocytes and duct cells; (8) to develop strategies to prevent and/or delay the onset of complications such as the targeted expression of growth factors; (9) to develop gene therapy approaches to alter the expression of receptors for advanced glycated endproducts; (10) to develop gene therapy methodologies to effectively treat various complications and validate them in relevant animal models; and (11) to develop carefully designed pilot clinical gene therapy studies for diabetic complications.

1016 TYPE 2 DIABETES GENETIC LINKAGE ANALYSIS CONSORTIUM

FY 2001 Action

Two expansions of the International Type 2 Genetic Linkage Analysis Consortium are planned for FY 2001. The first goal is to increase the number of African American samples genotyped that are available to the consortium for analysis. The NIDDK has identified an additional 800 African American samples to have genotyped and have applied to the Center for Inherited Disease Research (CIDR) to genotype these samples. By adding these samples to the Consortium, the African Americans can be studied as a subgroup for diabetes susceptibility genes that may exist uniquely in this ethnic group. The second goal is to follow up the combined linkage analysis on chromosome 20 and proceed with fine mapping of potential susceptibility genes. This effort would involve a coordinated fine mapping effort among the six groups involved in the Consortium that have evidence of linkage on chromosome 20.

Background

In 1997, a group of investigators studying type 2 diabetes, decided to form the International Type 2 Genetic Linkage Analysis Consortium to combine the data from multiple genome scans. The group started with an analysis of chromosome 20. This analysis suggested that there was more than one locus on chromosome 20 linked to type 2 diabetes in the Caucasian population. This study was used as the preliminary data for an R01 application that was submitted in 1998 to study the remaining chromosomes. The grant consisted of 11 research groups, with three of these groups from Europe. In addition, Glaxo and the NIDDK Phoenix Epidemiology and Clinical Research Branch continues to participate, but does not receive compensation from the grant. The application was converted to a U01 to allow for staff involvement and more flexibility in funding. The grant was awarded in August 1999.

Research Goals and Scope

In FY 2000, we used additional funds to increase the number of African American samples available for analysis. An application was submitted to CIDR to genotype an additional 800 samples. If it is favorably received, these samples should be genotyped in the fall. Additional funds may be required in FY 2001 to support the genotyping if the NIDDK does not join CIDR or if the final financial arrangement includes a per genotype fee.

Since the combined genome scan for chromosome 20 suggests at least one and probably two loci contributing to diabetes, it would seem that a coordinated effort to locate this gene or genes would be cost effective. There are six groups with evidence of linkage on 20. Since the peaks are very broad, the most likely location of diabetes genes is not obvious. Several groups have started to identify all the genes on chromosome 20q and to identify SNPs. A coordinated effort to identify and share SNPs and the location of genes on this chromosome has been proposed as an expansion of the linkage consortium. This model could be used in the future for other chromosomal locations that show evidence for linkage after a combined analysis.

1017 NIDDK CO-SPONSORSHIP OF BYPASS ANGIOPLASTY REVASCULARIZATION INVESTIGATION II CLINICAL TRIAL

FY 2001 Action

NHLBI's Bypass Angioplasty Revascularization Investigations (BARI) II Diabetes Trial will examine the impact on mortality and clinical cardiovascular events of: (1) early elective revascularization plus optimal medical therapy (versus optimal medical therapy alone); and (2) glycemic control primarily based on insulin-sensitizing drugs (versus insulin providing drugs) in type 2 diabetics with ischemic heart disease. The NIDDK will provide financial support for and scientific collaboration for this trial beginning in FY 2001 and for the six-year subsequent duration of the trial. The fundamental aim of the NHLBI/NIDDK collaboration is to strengthen its core science and to enhance its statistical power to detect a difference between the alternate strategies of glycemic control. This collaboration will build on the existing NHLBI/NIDDK collaboration on the ACCORD and SHOW trials, and will help assure methodologic consistency and comparability of results across all three studies.

Background

BARI-II is a 2x2 factorial multi-center trial designed to compare alternative treatment strategies in type 2 diabetics with significant but stable coronary artery disease. The trial will compare early versus deferred revascularization and will compare intensive glycemic control (HbA1c less than 7.5) using an insulin-sensitizing versus an insulin-augmenting treatment strategy. The investigators plan to enroll 3,000 patients, of whom 30 percent are expected to be minorities, at approximately 40 to 50 clinical sites, and to follow them for an average of five years. The primary outcome measure will be five-year mortality with secondary measures including myocardial infarction and other cardiovascular events, PAI-1, and other cardiovascular disease risk factors, as well as quality-of-life measures. The study timetable includes six months for start-up (protocol finalization, forms development, training), two years for recruitment, four additional years for follow-up, and six months for close-out, for a total study duration of seven years beginning in September 2000.

Research Goals and Scope

NIDDK support will be used to add measurement of urinary albumin to the study protocol that was not included in the budget allocated by NHLBI. This provides an opportunity to investigate the relationship between proteinuria and cardiovascular outcomes in a racially diverse population with well-controlled lipids, blood pressure and glycemia. NIDDK co-sponsorship will provide partial support to expand the BARI II Diabetes Trial from 2,600 to 3,000 patients. The expanded study population will allow the investigators to retain the originally proposed creatinine exclusion criterion of greater than 2.0, although one of the insulin-sensitizing drugs, metformin, is contraindicated for creatinine levels greater than 1.5. They have estimated that 5 to 10 percent of BARI II diabetes patients will be unable to take metformin at baseline (the percentage will increase as the study progresses) and that a substantial proportion of those patients will be unable to reach their HbA1c goal without adding an insulin-providing drug. The additional 400 patients will provide a buffer to assure satisfactory power in the face of

this anticipated "crossover." They may also provide additional power to detect a treatment effect slightly smaller than the 25 percent upon which the original 83 percent power estimate was predicated.

1019 EPIDEMIOLOGY OF DIABETES INTERVENTIONS AND COMPLICATIONS GENETICS STUDY

FY 2001 Action

The Epidemiology of Diabetes Interventions and Complications (EDIC) study is being supplemented to expand earlier family study analyses to identify candidate gene polymorphisms that influence susceptibility to retinal and renal complications of type 1 diabetes. DNA and data on diabetic complications will be obtained from parents, siblings, and EDIC probands so that family-based association studies can be performed. The Diabetes Research Working Group identified the study of the genetics of diabetes and its complications as an extraordinary opportunity for research planning by the NIDDK.

Background

The Diabetes Control and Complications Trial (DCCT) was a clinical trial conducted in 1,441 patients with type 1 diabetes that studied the health benefits of intensive versus conventional treatment of blood glucose levels. The subjects were recruited during 1983 through 1989 and were studied for an average of 6.5 years, with extensive data obtained on diabetes treatment, glucose and glycosylated hemoglobin levels, and ophthalmic, nephropathic, neuropathic, neuropsychological, macrovascular, and quality-of-life outcomes. In 1993, the DCCT was stopped because of compelling evidence that intensive therapy significantly delayed the onset and slowed the progression of diabetic retinopathy, nephropathy, and neuropathy. The DCCT participants are subsequently being studied through EDIC and are no longer randomized to intensive or conventional treatment, but are being followed to examine the association of glycemic treatment and risk factors with the later term complications of diabetes. Participant retention is greater than 90 percent.

From 1991 through 1993, a family study was performed in a subgroup of the DCCT/EDIC cohort and in first-degree relatives of the cohort who were identified to have either type 1 or type 2 diabetes. The study found that the prevalence of severe retinopathy clustered in families and confirmed the results of other studies that there was familial clustering of nephropathy. In addition, white blood cells from the DCCT/EDIC probands and relatives with type 1 diabetes have been immortalized and deposited in the repository of the Human Biological Data Interchange, along with clinical data, for use by the scientific community.

The NIDDK has since convened several meetings with experts in genetics, epidemiology, and statistics to advise the Institute and the DCCT/EDIC study group on the most appropriate use of the DCCT/EDIC cohort for additional genetic studies. Further genetic studies in the DCCT/EDIC were encouraged by the group of experts and the group continues to provide guidance while the genetic study protocol is being developed and implemented.

Research Goals and Scope

DNA samples and data on diabetic complications will be obtained from affected (type 1 and type 2 diabetic) siblings of DCCT/EDIC probands. DNA samples will also be obtained for all parents of probands and one unaffected sibling. If at least one parent of each proband is not available, DNA will be obtained on all available unaffected siblings. Additional phenotypic information will be collected to be consistent with other ongoing genetic studies of diabetic complications, such as FIND and GOKIND. A family-based association study using the Transmission/Disequilibrium Test (TDT) will be done initially at the extremes of the distribution of complications (e.g., existence of complication with short duration of diabetes vs. no complication with long duration of diabetes). Established functional candidate genes (e.g., those associated with type 1 or 2 diabetes, associated with complications, those based on animal studies) will be examined. If an association is found with the extremes of the distribution of complications, then all families will be analyzed. Associations will be adjusted for other covariates such as age, sex, duration of diabetes, and glycemic control. If associations are found in these analyses, then more novel polymorphisms may be examined as a next step. Finally, cell lines from these studies will be made available to the scientific community in a reasonable time frame after these planned analyses have been completed by the DCCT/EDIC Study Group.

1021 METHODS TO ENHANCE PROCUREMENT AND RAPID UTILIZATION OF HUMAN PANCREATA FOR ISLET ISOLATION AND/OR TRANSPLANTATION

FY 2001 Action

To improve pancreas procurement for both pancreas and islet transplants, an initiative using the SBIR contract mechanism is proposed. This initiative would request contract proposals for the development of Human Leukocyte Antigens (HLA) analyses that take one hour or less and can be done on blood; the development and validation of training methods to enhance the ability of Organ Procurement Centers to harvest the pancreata; and application of DNA array technology to rapidly ascertain the quality of islet preparations prior to transplantation.

Background

Pancreas transplants are now almost as successful as kidney transplants and are appropriate therapy for patients with diabetes requiring a kidney transplant. Unfortunately, the majority of pancreata available for organ collection are not collected. In 1995, the United Network for Organ Sharing (UNOS) reported harvesting 4,997 cadaveric kidneys but only 1,288 cadaveric pancreata. Of the pancreata procured, only 80 percent could be used for pancreas transplantation.

In addition, Dr. James Shapiro and colleagues from the University of Alberta, Edmonton, Canada, have shown recently that islet transplantation can be successful using an immunosuppression protocol that does not include glucocorticoids. If these results are reproduced in studies soon to be conducted at multiple centers, there will be an even greater demand for pancreas procurement.

Research Goals and Scope

Research areas relevant to improved pancreas procurement for both pancreas and islet transplantation may include:

A. Development and validation of a training syllabus to increase the number of individuals qualified to retrieve pancreata.

B. Development of a rapid method to accurately determine the organ donors' HLA type. This new method should utilize blood, instead of lymph nodes, and should meet the certification requirements of the American Society of Histocompatibility Laboratories.

C. Utilization of DNA array technology to ascertain the quality of an islet preparation. Presently, there are no accurate predictors for which islet preparations will survive upon transplantation. Thus, the application of this technology will require the investigators to develop collaborations with transplantation centers to verify the utility of their assay.

1022 AND 1023 EXPAND NDEP MEDIA CAMPAIGN AND OTHER NDEP MESSAGES AND DEVELOP RESOURCES AND TRAINING MATERIALS FOR HEALTH CARE PROVIDERS

FY 2001 Action

The National Diabetes Education Program (NDEP) is a joint program of the NIDDK and the Centers for Disease Control and Prevention, and has 200 public and private sector partners. The purpose of the program is to improve the treatment and outcomes for people with diabetes, to promote early diagnosis and, ultimately, to prevent the onset of diabetes. The participation of representatives of African American, Hispanic/Latino, Native American/Alaska Native, and Asian and Pacific Islander communities is a key feature of the NDEP Partnership. The NIDDK plans to develop additional media strategies to increase awareness of the seriousness of type 2 diabetes and understanding of diabetes and its control, and to promote a unified approach to diabetes care among minority populations with diabetes, health care providers, audiences at risk or undiagnosed, payers, health care purchasers, and policy makers. The NIDDK will also develop community interventions specific for minority populations through trusted and valued community channels and organizations that promote healthy lifestyle behaviors for diabetes care and will promote health care policies that improve quality and access to diabetes care for minority audiences.

Background

The NDEP takes a multi-component approach to address its goal to improve the treatment and outcomes for people with diabetes. These components include public awareness and education campaigns, special population approaches, community-based interventions, health systems changes, and an inclusive partnership network. Strategies and activities are being implemented in each of these component areas through established partner-based work groups that provide guidance, direction, and resources. Specific work groups representing each targeted minority population have been created to assist the NDEP in developing strategies, activities and products that are culturally and linguistically appropriate and to disseminate the materials to their communities. NDEP is an initiative in the NIDDK Strategic Plan on Minority Health Disparities.

The NDEP is currently conducting a series of diabetes awareness campaigns using the theme, "Control Your Diabetes For Life." to encourage people with diabetes to manage their diabetes to live healthier lives. The campaigns target general audiences and the populations disproportionately affected by diabetes, namely, African Americans, Hispanic/Latinos, Asian Americans and Pacific Islanders, Native Americans, and senior citizens. The campaigns include television, radio and print public service announcements, educational materials, and information kits for the media and communities. The NDEP is currently developing campaigns for health care providers to encourage them to work with their patients to improve glucose control, and to identify, diagnose, and treat children with type 1 and type 2 diabetes.

For diabetes messages to reach communities, the NDEP has developed a Partnership Network of over 200 organizations from the national, state and local levels. These partners are valued and trusted community channels and serve as a dissemination vehicle for NDEP information and messages. The NDEP has created a Community Partnership guide, and a video and training module that provide tools, resources and information to assist individuals and organizations to implement diabetes activities in their communities. Interventions for minority populations using nontraditional partners to promote healthy lifestyle behaviors and help improve diabetes care in communities are currently being developed.

Research Goals and Scope

The purpose of the NDEP is to improve the treatment and outcomes for people with diabetes, to promote early diagnosis, and, ultimately, to prevent the onset of diabetes. The NDEP's objectives are: (1) to increase public awareness of the seriousness of diabetes, its risk factors, and potential strategies for preventing diabetes and its complications; (2) to improve understanding about diabetes and its control and to promote better self-management behaviors among people with diabetes; (3) to improve health care providers' understanding of diabetes and its control and to promote an integrated approach to care; and (4) to promote health care policies that improve the quality of and access to diabetes care. The NDEP will continue to develop and promote diabetes messages that reflect the newest scientific evidence about diabetes control, treatment and prevention. The NDEP may expand its target audiences to include those people who can benefit from the scientific results. The NDEP will continue to foster relationships with new partners, especially non-traditional partners such as the faith community, to increase NDEP's reach to its target audiences. Furthermore, the NDEP will develop innovative community interventions for minority populations that promote healthy lifestyle behaviors and help improve diabetes care in communities.

1024 DIABETES PREVENTION PROGRAM EXTENSION

FY 2001 Action

The Diabetes Prevention Program (DPP) is a multi-centered randomized trial to determine whether type 2 diabetes can be prevented or delayed in a population of high-risk individuals based on impaired glucose tolerance status. The DPP includes two active treatment groups (metformin and life-style) and placebo controls with an average follow-up of 4.5 years. The study began in July 1994 with a project period, limited by RFA policy, of seven years. Based on protocol design and bio-statistical considerations, the DPP design will require a total of nine years to complete participant treatment/follow-up and conclude data analysis and reporting.

Background

The enormous human and economic burden that accompanies type 2 diabetes mellitus, and the difficulty of treating it effectively once it has developed make it an appropriate target for prevention or delay. In 1993, the NIDDK issued an RFA for proposals for a study with the objective of preventing or delaying the development of type 2 diabetes in adults. A major emphasis was placed on minority communities in which type 2 diabetes is disproportionately prevalent. Clinical centers were selected in 1994, and protocol development began in August 1994 with the initiation of a three phase process: Phase 1--planning; Phase 2--recruitment and intervention; and Phase 3--close out, data analysis, and reporting. Phase 1 was concluded in January 1996, with approval of the DPP Protocol by the Data Monitoring Board, and concurrence by the NIDDK. Recruitment of participants began in July 1996 and was completed in June 1999 with the enrollment of 3,234 volunteers in the three-arm study with participant follow-up to continue until June 2002. Data analysis and reporting of the primary study results will conclude in June 2003. A extension of the study through June 2003 was approved by the NDDK Advisory Council at the May 2000 meeting.

Research Goals and Scope

The goal of this DPP extension is to allow for an adequate duration of participant treatment and follow-up to meet the design and bio-statistical requirements of this study. These are to provide 90 percent power to detect a 33 percent reduction in the progression to diabetes for the active intervention groups compared to the progression to diabetes in the control group.

1027 TYPE 1 DIABETES GENETIC CONSORTIUM

FY 2001 Action

The NIDDK and the Juvenile Diabetes Foundation International are planning a meeting to explore the establishment of a Type 1 Diabetes Genetic Consortium. Three genome-wide scans for type 1 diabetes have recently been completed and have identified several loci as harboring a diabetes susceptibility gene. A combined analysis of these three datasets could identify the most promising loci. This meeting is tentatively scheduled for November 20, 2000. Depending on the outcome of the meeting, the NIDDK could provide support for planning for such a consortium grant through administrative supplements.

Background

In 1998, two studies were published on genome-wide scans for type1 diabetes. These studies were conducted on relatively few samples and the two studies did not confirm the location of diabetes susceptibility genes. Both groups have since typed additional patients, and a third group has now completed an independent study. With these three studies combined, there are approximately 1,500 diabetic sib pairs. Investigators believe that with this larger combined dataset that identification of loci is possible and fine mapping of these loci should begin.

Research Goals and Scope

Several groups have expressed interest in a coordinated effort to identify putative type 1 diabetes genes. The combined genome scans will likely identify several possible locations for diabetes susceptibility genes. A Consortium approach to apportion the work among several groups will prevent redundancy and increase the likelihood of finding diabetes susceptibility genes. If these groups are agree to collaborate at the upcoming meeting, we will provide support for creation of a common database and other analyses needed to foster this Consortium effort.

1029 ISLET/BETA CELL TRANSPLANT REGISTRY (RFP DK-00-002)

FY 2001 Action

The objective of this project is to establish a North American islet/beta cell transplant registry that will collect and analyze data both pre- and post-transplantation from all institutions performing these transplants within North America. To be included in this registry will be patient demographics, patient and graft survival rates by area, surgical technique, type of immunosuppression, immunoisolation and/or tolerance induction protocol, donor source, tissue typing, assessment of viral and bacterial contamination in donor tissue, length of graft preservation, implantation site, islet/beta cell preparation procedure and islet/beta cell storage procedure. Metabolic data will also be collected and analyzed. In addition, the data and the results of analyses will be communicated to the scientific community.

Background

On October 9, 1984, the NIDDK sponsored a one-day workshop on segmental pancreas and islet transplantation. Dr. Paul Lacy, Washington University School of Medicine, chaired the meeting, which brought together eleven of the leaders in this field. While several research needs were identified, every workshop participant concurred that the maintenance of a detailed registry of all transplant recipients is essential for the development of this research. At the World Conference on Diabetes Research held in November 1985 (sponsored by the Juvenile Diabetes Foundation International, the World Health Organization and the NIDDK) this recommendation was reiterated on a worldwide basis by groups of international research leaders.

As a result of these recommendations in 1989, the NIDDK began funding The International Pancreas Transplant Registry (IPTR), which was established in 1980 by Dr. David Sutherland, University of Minnesota.

As part of the IPTR, Dr. Sutherland had entered into a collaborative arrangement with Dr. Konrad Federlin, from the University of Giessen in Germany. Dr. Federlin had instituted an International Islet Cell Transplant Registry. He has focused his efforts on the collection of islet transplant data from throughout the world using forms similar to those of the International Pancreas Transplant Registry. Dr. Sutherland has furnished Dr. Federlin with all the islet transplant data in the IPTR and continues to provide him with prospective information. In exchange, Dr. Federlin furnishes Dr. Sutherland with updates on his islet transplant registry.

With the significant expansion of islet/beta cell transplantation within the U.S., it would be extremely beneficial to collect the results of islet/beta cell transplants performed in North America. This would enable the collection of considerably more information on these transplants. In April 1999, an Advisory Committee to the Division of Diabetes, Endocrinology and Metabolic Diseases, NIDDK recommended the establishment of an Islet/Beta Cell Transplant Registry.

Research Goals and Scope

This initiative encompasses the establishment of the Islet/Beta Cell Transplant Registry and the provision of statistical, clinical coordination, technical, regulatory, and administrative support for the Registry to collect information on islet or beta cell transplants in patients within North America. This registry will serve as a research tool for the medical community. It is envisioned that this contract will address fundamental questions pertinent to the improvement of host and graft survivals following islet/beta cell transplantation.

1030 DIABETES RESEARCH CENTERS--EXTENSION OF THREE CENTERS AND ENHANCEMENT OF CENTERS PRGRAM

FY 2001 Action
The NIDDK will provide administrative supplements to provide four-month extensions to two Diabetes Endocrinology Research Centers (DERC) and one Diabetes Research and Training Center (DRTC). This will permit these applications to undergo secondary review at the February 2002 rather than the September 2001 National Advisory Council meeting.

Background
The NIDDK currently supports eight DERCs and six DRTCs. It is NIDDK policy to foster competition for these center awards by issuing an RFA each time an existing center is due to compete. To enhance competition and efficiently utilize peer review, project periods have occasionally been extended for individual centers to allow a common receipt date for several centers. NIDDK generally competes three to five existing centers at the same time. Because initiatives to be funded in a given fiscal year must receive secondary review no later than the September National Advisory Council meeting, the workload for the NIDDK Review Branch is generally greatest during the review cycle involving September secondary review. To provide flexibility to issue research solicitations after the appropriation of the Institute's budget, which can then be funded in that fiscal year, it is desirable to move other solicitations, particularly those that require recurring Institute review into a review cycle that does not involve the September Council. It is to distribute the NIDDK Review Branch workload that these awards will be extended.

The Diabetes Research Working Group recommended that the Diabetes Centers Program should be strengthened. To consider how this might best be accomplished, the Institute will convene a Diabetes Centers Directors meeting November 27-28, 2000. The first day will involve a meeting of DRTC directors and the directors of the Demonstration and Education components of the DRTCs with leaders in diabetes research translation. The second day will involve a joint meeting of DERC and DRTC directors to consider how to enhance the cores and pilot and feasibility programs that are common to both types of center and to identify other components that could be of value in enhancing diabetes research. This meeting will address steps the NIDDK can take to enhance translation research, including a discussion of improved efforts to address health disparities in minority populations disproportionately affected with diabetes.

Research Goals and Scope
The NIDDK Diabetes Centers Programs has been in existence for 23 years. This is an appropriate time to evaluate this program, identify those aspects that have been most successful and consider how the centers program should be modified in the light of changing research needs and opportunities.

DIVISION OF DIABETES, ENDOCRINOLOGY AND METABOLIC DISEASES
Conferences and Workshops

Vitamin E for the Prevention of Diabetic Complications
October 23, 2000

The NIH will convene a workshop on October 23, 2000, to determine whether there is compelling evidence to support the design of a large-scale clinical trial to use vitamin E to prevent diabetic complications. Leading investigators in the field will present available animal and human data regarding the use of vitamin E in the prevention of diabetic complications. In addition, the results of large-scale clinical trials of vitamin E to prevent cardiovascular disease and cancer will be reviewed. An expert panel will analyze the data presented and provide advice regarding appropriate next steps.

Diabetes Centers Meeting
November 27-28, 2000

The Diabetes Research Working Group recommended that the Diabetes Centers Program should be strengthened. To consider how this might best be accomplished, the Institute will convene a Diabetes Centers Directors meeting November 27-28, 2000. The first day will involve a meeting of directors of Diabetes Research and Training Centers (DRTC) and the directors of the Demonstration and Education components of the DRTCs with leaders in diabetes research translation. The second day will involve a joint meeting of Diabetes Endocrinology Research Centers (DERC) and DRTC directors to consider how to enhance the cores and pilot and feasibility programs that are common to both types of center and to identify other components that could be of value in enhancing diabetes research. This meeting will address steps the NIDDK can take to enhance translation research, including a discussion of improved efforts to address health disparities in minority populations disproportionately affected with diabetes.

Depression and Mental Disorders in Diabetes, Renal Disease, and Obesity/Working Group Conference
January 2001

This meeting will be held in cooperation with the National Institute of Mental Health and Office of Behavioral and Social Sciences Research will present findings on the relationship between depression and related mental disorders, and chronic diseases including, diabetes, renal disease, and obesity. Presentations will focus on areas ranging from the epidemiology, biology, and behavioral risk factors and protectors for depression and chronic diseases through racial and ethnic disparities. The conference was recommended by advisory researchers from multiple disciplines who met with representatives from the NIDDK and the National Institute of Mental Health on March 17 and July 17, 2000, to discuss research needs in the field of depression and outcomes of diabetes, renal disease, and obesity.

Diabetes and Aging: From Basic Biology to Clinical Care
Bethesda, MD
January 2001

In cooperation with the National Institute of Aging, the NIDDK is holding a meeting of the Diabetes Mellitus Interagency Coordinating Committee (DMICC) on "Diabetes and Aging: From Basic Biology to Clinical Care." This meeting will bring together researchers in the genetic, environmental, phenotypic, and pathogenic causes of type 2 diabetes during the aging process. It will also bring together researchers looking at diabetes health care among the elderly including disparities in diabetes treatment among minority groups during the aging process. In addition, DMICC member Federal Agencies will report on their efforts in the treatment and clinical management of older individuals.